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Reply

We appreciate the comments of Dr. Joshi and colleagues regarding our report on the cardiovascular risk assessment of candidates for liver transplantation (1).

We agree that liver transplantation in patients with severe left ventricular systolic dysfunction carries a higher risk for cardiovascular complications and mortality. These patients should be thoroughly evaluated, as we have described, and would benefit from referral to higher volume transplantation centers with experience in caring for such patients. As noted in our report, and by Joshi et al., there have been case reports of successful transplantation in such patients, often requiring combined liver and heart transplantation (2). Several potential etiologies of systolic dysfunction in patients with end-stage liver disease have been described, and some may be reversible (3,4). Therefore, we do not consider severe systolic dysfunction to be an absolute contraindication to liver transplantation. However, liver transplantation in this patient type should be undertaken only at centers with advanced heart failure programs.

With regard to the utility of the measurement of oxygen consumption at peak exercise to assess aerobic capacity, this is certainly another piece of information that can be added to the cardiologist's armamentarium when performing a cardiovascular risk assessment of a liver transplantation candidate. In a multivariate analysis, it was associated with 1-year survival and was also associated with post-operative complications in sicker patients (5). Although we do not believe that this should be a sole reason for exclusion for liver transplantation candidacy, we agree that it may aid in assessing cardiovascular risk.

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doi:10.1016/j.jacc.2011.09.029

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The Role of Platelet Function Testing and Genotyping in the Stented Patient Treated With Clopidogrel

We read with interest the study of Campo et al. (1). Their observation that $P2Y_{12}$ reaction units (PRU) decreased at 1 month compared to baseline in patients receiving clopidogrel undergoing percutaneous coronary intervention (PCI) is similar to our report in 2003 (2), where ~30% of patients were resistant at 1 and 5 days post-PCI, and 15% were resistant at 30 days. Similar observation of lower prevalence of 30-day high platelet reactivity compared to 12 to 24 h post-stenting was also reported recently (3). We further presented similar PRU levels at 24 h after 600 mg loading and just before the last maintenance dose at 6 weeks (4). Mean PRUs at 8 h after last maintenance dose decreased by ~25. These findings indicate the "booster" effect of the last maintenance dose by new active metabolite generation. Therefore, clopidogrel response is significantly influenced by measured time after clopidogrel administration even during the maintenance phase. In the study by Campo et al. (1), a decrease in PRU levels at 1 month may be partially related to measured time (~25 PRU in stable patients). However, Campo et al. (1) did not mention the timing of measurements with respect to the last dose administration.

Another important issue is that the post-PCI event occurrence reported by Campo et al. (1) is relatively discordant with most PCI-related studies demonstrating more frequent events within 30 to 60 days post-PCI. Interestingly, the first ischemic event in Campo et al. (1) occurred at ~50 days post-PCI (estimated from Fig. 3 of Campo et al. [1]).

In multivariate analysis, *CYP2C19*17* variant and 30-day PRU together were independent determinants of bleeding, implicating that *CYP2C19*17* effect on bleeding may be independent of clopidogrel response, which requires further explanation. Although platelet function testing and genotyping may play complementary roles in tailoring antiplatelet therapy, numerous clinical factors including drug-drug interaction may influence the magnitude of platelet reactivity and clinical outcomes. In the future, a comprehensive algorithm including clinical as well as laboratory findings may optimize outcomes in the era of potent $P2Y_{12}$ inhibitors.

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